Overdiagnosis in breast imaging

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Abstract

The main harm of overdiagnosis is overtreatment. However a form of overdiagnosis also occurs when foci of cancer are found by imaging in addition to the symptomatic lesion when this leads to additional treatment which does not benefit the patient. Even if overtreatment is avoided, knowledge of the diagnosis can still cause psychological harm.

Overdiagnosis is an inevitable effect of mammographic screening as the benefit comes from diagnosing breast cancer prior to clinical detectability. Estimates of the rate of overdiagnosis at screening are around 10%. DCIS represents 20% of cancers detected by screening and is the main focus in the overdiagnosis debate. Detection and treatment of low grade DCIS and invasive tubular cancer would appear to represent overdiagnosis in most cases. Supplementary screening with tomosynthesis or US are both likely to increase overdiagnosis as both modalities detect predominantly low grade invasive cancers. MRI causes overdiagnosis because it is so sensitive that it detects real tumour foci which after radiotherapy and systemic therapy do not, in many cases go on and cause local recurrence if the women had had no MRI and undergone breast conservation and adjuvant therapy with these small foci left in situ.

Key Words

Breast imaging; overdiagnosis; mammography; tomosynthesis; ultrasound

Key points

1. Overdiagnosis is an inevitable effect of mammographic screening

2. Detection of low grade DCIS and tubular cancer usually represents overdiagnosis

3. Supplementary screening with tomosynthesis or US will increase overdiagnosis

Introduction

Overdiagnosis is when disease is found which if left undiagnosed would not present clinically in the patient's lifetime. Breast imaging can result in overdiagnosis of invasive cancers, DCIS and benign lesions of uncertain malignant potential. The main harm of overdiagnosis is overtreatment, i.e. women have surgery, radiotherapy and/or systemic therapy for disease which would not cause harm in their lifetime. A form of overdiagnosis also occurs when foci of cancer are found by imaging in addition to the symptomatic lesion when this leads to additional treatment which does not benefit the patient. This is particularly an issue when using breast MRI prior to breast conserving surgery. However a similar situation can occur in women who have imaging follow-up after a poor prognosis cancer which will eventually kill the patient, and mammographic follow-up detects impalpable good prognosis breast cancer elsewhere in the ipsilateral or the contralateral breast.

Overtreatment is not the only harm of over-diagnosis. Even if overtreatment is avoided, knowledge of the diagnosis can cause psychological harm to the patient and their family. Overdiagnosis can also cause practical problems like difficulties obtaining a mortgage or life and travel insurance.

Overdiagnosis in mammographic screening

Overdiagnosis is an inevitable effect of mammographic screening as the benefit comes from diagnosing breast cancer prior to clinical detectability. The harms of such overdiagnosis have to be balanced against the benefits of a reduction in breast cancer mortality of about 20% in those women invited for screening (1). The other major harm of screening come from false positive results. Since the harms and benefits are not directly comparable, the only way to balance them is to seek the opinion of women who are invited for screening after they are made aware of the issues. Overdiagnosis is a difficult concept to explain to non-medically trained people. Qualitative research would appear to be key in this context but few resources have been spent in this way. Work that has been done suggests that women are surprised by the frequency of overdiagnosis which occurs but that the impact on the intention of women to attend for screening is small (2,3).

Over diagnosis is also complicated by the lack of agreement on how and when to calculate overdiagnosis. If overdiagnosis is measured immediately after screening ceases then estimates will be very high as all the lead time achieved will be expressed as over diagnosis. However, if overdiagnosis is measured 10 years after screening ceases or at death so allowing the compensatory drop in incidence to occur once screening ceases, then estimates will be lower, and true over diagnosis will measured or estimated. Estimates of the rate of overdiagnosis if a compensatory drop is taken into account in most studies are around 10% (4-5). The overdiagnosis rate when screening women aged 40-49 is as low as 1% (6). Overdiagnosis becomes commoner when screening older women as more women die with breast cancer rather than of breast cancer as decreased life expectancy and more indolent invasive breast cancer biology combine.

DCIS and over diagnosis

DCIS represents 20% of cancers detected by screening and is the main focus for many in the overdiagnosis debate. Mammography has a high sensitivity for high grade DCIS with necrosis as such

disease readily calcifies, but low sensitivity for detecting low grade DCIS as often such disease does not calcify (7). This explains why 70% of screen detected DCIS is high grade. This means that DCIS detection and treatment at screening will differentially prevent the occurrence of high grade invasive cancers since high grade DCIS is associated with high grade invasive cancers. This should lead to benefits in a short period and not be associated high rates of over diagnosis. However this does not mitigate the harms due to overdiagnosis caused by the detection of low grade DCIS which represents about 15% of screen detected DCIS and 3% of all screen detected cancer. Many such cases represent overdiagnosis. The LORIS trial which randomises women between surgical therapy and active monitoring continues to be an important study which deserves the support of those working in screening (8).

A recent study has shown an association between DCIS detected at screening and a reduction in invasive interval cancers in the following three years. The short time interval in which this effect is shown demonstrates that high grade DCIS (which represents the majority of screen detected DCIS) has the potential to become invasive and symptomatic in a short time period. What has not been addressed by this paper is the effect of DCIS detection on invasive cancer detection at the subsequent screening round and beyond (9). Detection of DCIS at screening is therefore helpful for the majority of women but causes overdiagnosis in a minority. Reducing this harm by not over-treating cases of screen detected low grade DCIS must remain a priority.

How different terminology for ductal carcinoma in situ (DCIS) impacts on women's concern and management preferences is also an important issue. A qualitative study found that communicating a diagnosis of DCIS using terminology that does not include the cancer term was preferred by many women and may enable discussions about more conservative management options (10).

Tubular cancer

Tubular cancers are excellent prognosis invasive cancers which represent about 2% of symptomatic invasive cancers and 10% of screen detected invasive cancers. A large study has shown that breast cancer death only occurs if women who have had a tubular cancer develop a subsequent more aggressive cancer (11). Another study found women with tubular cancer to have the same survival as women with DCIS with no breast cancer deaths in the follow-up period (12). These finding are surprising as about 5% of women with tubular cancer have axillary metastases. Unless tubular cancer undergoes phenotypic drift and develops into less differentiated cancers if left in situ, then detecting tubular cancers at screening will have no impact on breast cancer mortality and will represent overdiagnosis in the majority of cases, as symptomatic tubular cancers are rare. However many ductal cancers on no specific type have a tubular component suggesting they may have arisen from a tubular cancer. The frequency of tubular carcinoma de-differentating into a more aggressive cancer if left in situ is currently unknown. Tubular cancers are currently treated in the same way as other invasive cancers with whole breast radiotherapy following wide local excision. This appears to represent overtreatment.

Tomosynthesis and overdiagnosis

Digital Breast Tomosynthesis (DBT) is a new three-dimensional breast imaging technique using upgraded digital mammography equipment and software to present a series of “slices”, similar to MRI and CT scans. DBT technology is designed to overcome the problem of overlapping tissue on mammograms and potentially improve the ability to diagnose both abnormal and normal breasts. DBT involves taking multiple images of the breast from different angles, which are then digitally reconstructed into “slices”.

Recent studies have shown that in a screening setting DBT detects more cancers than full field digital mammography (FFDM)(13,14) and in units with high recall rates DBT also lowers recall rates. No randomised controlled trial of mammography vs DBT has been performed so the effect of screening with DBT on breast cancer mortality is unknown. Nearly all the cancers detected by DBT but not diagnosed on FFDM are found because subtle spiculate lesions are identified on the DBT images. Spiculation is a feature of low grade invasive cancers and is uncommon in grade 3 cancers. So it is not surprising that the additional cancers identified by DBT are mainly grade 1 and 2 invasive cancers. Even when histological grade is taken into account in a multivariate analysis spiculation maintains an independent good prognostic effect (15). This may be because basal like cancers spiculate less than other cancers even when corrected for grade, and basal like cancers are known to have a poor outcome (16).

This good prognostic profile of the additional cancers detected by DBT raises the possibility that screening with DBT will increase the rate of overdiagnosis compared with screening women with FFDM alone. The screening studies of DBT will be able to measure the interval cancer rate and compare this with the interval cancer rate prior to the introduction of DBT. If the interval cancer rate drops then one could argue that screening DBT is detecting at least some biologically important cancers and so may impact on breast cancer mortality. If the interval cancer rate remains unchanged then it could be argued that screening DBT is predominantly increasing overdiagnosis and is unlikely to impact on breast cancer mortality. A recent US study has shown a trend towards a lower interval cancer rate following the introduction of tomosynthesis screening (17).

Ultrasound (US) screening and over diagnosis

Screening women with mammographically dense breasts using bilateral US has many advocates. This is because mammographic sensitivity is reduced in women with dense breasts and breast density is also a significant risk factor for breast cancer (18). The masking effect of breast density means that in women with dense breasts, the lead time of screening is shortened and the mean size of cancers detected is larger (19). One issue is the lack of a standardised definition of a dense breast, since visual breast density assessment has very poor reproducibility (20). Supplementary screening with US has been shown to significantly increase the invasive cancer detection rates and most of the additional cancers detected are small and node negative. Only about 10% of additional cancer detected by US screening are DCIS. The downside of supplementary US screening is the very poor specificity and the time needed to scan both breasts. Less than 1 in 10 US screening provoked biopsies shows cancer. There are no RCT trials of supplementary US screening designed to measure breast cancer mortality.

To what degree are the additional cancer detected by supplementary US screening likely to contribute to additional overdiagnosis? A recent RCT has shown that such screening significantly reduces the interval cancer rate, implying that at least some of the cancers detected by US screening are biologically important (21). Unfortunately this study did not publish the grade distribution of the additional cancers detected by US screening, which would have helped assessment of possible overdiagnosis. A previous Italian study showed a similar drop in interval cancer rates in women given supplemental ultrasound screening (22). On the other hand, in the ACRIN 6666 Trial almost half (46%) of the additional invasive cancers found were grade 1 compared to 19% of those cancer detected by mammography alone and 25% of those detected by both modalities (23). This is not surprising as the US characteristics of low grade cancers are more suspicious than those of high grade cancers. So despite reducing interval cancer

rates, supplemental screening of women with dense breasts is likely to significantly increase overdiagnosis compared to women screened by mammography alone.

MRI and over diagnosis

Breast MRI is now widely used for high risk screening, assessing breast implants, monitoring neoadjuvant chemotherapy and local staging. Its widespread use to locally stage breast cancer prior to breast conserving surgery is controversial as the multicentre randomised controlled COMICE study showed that MRI use did not reduce re-operation rates (24). MRI use in this clinical setting has also been shown to be associated with increased mastectomy rates (25) but not a reduction in local recurrence or disease free survival (26, 27). The problem is not that MRI gives false positive results, but that it is so sensitive that it detects real tumour foci which after radiotherapy and systemic therapy do not, in many cases go on and cause local recurrence if the women had had no MRI and undergone breast conservation and adjuvant therapy with these small foci left in situ. Currently however it is impossible to tell which foci will or will not go on to cause local recurrence. So with current treatment protocols, many of the addition tumour foci detected by MRI represent over diagnosis as they lead to over- treatment. However MRI also gives the opportunity to give less treatment to women with truly uni-focal tumours. Intra-operative radiotherapy and partial breast irradiation are associated with less morbidity than whole breast radiotherapy so may be particularly appropriate in women who have a unifocal tumour on MRI. Unfortunately the TARGIT trial of intraoperative radiotherapy (IORT) did not use MRI to confirm true unifocality so this may be why the TARGIT-A trial has a higher local recurrence rate in women treated with IORT compared to those women given whole breast radiotherapy (28).

A recent study of staging MRI in older women has shown that an increased synchronous contralateral breast cancer detection rate, attributable to MRI, was not offset by a decrease of subsequent contralateral breast cancer occurrence among older women with early-stage breast cancer, suggesting that preoperative MRI in older women with breast cancer may lead to significant overdiagnosis (29).

MRI detects virtually all invasive breast cancers so the trend to preferential detection of low grade invasive cancers seen with mammography and ultrasound is not present with MRI. MRI also tends to identify high grade DCIS more than low grade DCIS so MRI detected DCIS is not a source of major overdiagnosis.

Conclusion

The use of any breast imaging technique can lead to overdiagnosis and overtreatment. Currently our ability to detect disease is not matched by our ability to predict disease behaviour. This leads to overtreatment in many cases. The harms of overdiagnosis need to balanced against the benefits of using imaging techniques. Knowing more is only helpful when you know what to do with the information gained. This is currently not always the case with breast imaging.

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